

REMARKS*Amendments*

The Claims are amended to correct grammar. These amendments do not alter the scope or meaning of the Specification and Claims and introduce no new matter.

Abstract

Our amendment canceling the first paragraph of the abstract, originally requested in our Response submitted Oct 12, 2005, is re-submitted above on a separate page.

Specification-Objections

The Specification includes a required "BRIEF" description of the drawings section at p.3-4; and more extensive descriptions of the same figures are provided at p.26-27.

No other drawings or flow diagrams are present in this application, but only three tables of chemical structures and related text at p. 28-31. Chemical structures are permitted in the specification (see e.g. 37 CFR 1.52 (b)(6): Non-text elements (e.g., tables, mathematical or chemical formulac, chemical structures, and sequence data) are considered part of the numbered paragraph...).

Double Patenting

Upon allowance of an overlapping claim in the cited 10/677,733 application, a terminal disclaimer will be filed.

35USC112, second paragraph

Applicants submit that the claims are definite: applicants anticipate that the most immediate commercial embodiment of the claimed method is to screen for ligands as proposed in the Action; however the claims are not written nor intended to be avoided by practicing the method with a known ligand rather than a library of non-established ligands.

35USC112, first paragraph (enablement)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface

binding specificity of the PAS domain, wherein ...the binding specificity is an intramolecular binding affinity of the PAS domain, detected as a change in chemical shifts detected by $^1\text{H}/^{15}\text{N}$ -HSQC NMR.

As explained in the Specification, suitable foreign ligands may be screened from libraries of synthetic or natural compounds, and conventional SAR analyses provide ligands of higher affinity and/or specificity (Specification, p.6, lines 9-10). This process was specifically exemplified with HIF2a PAS B, wherein a library of 772 compounds (Specification p.13, lines 6-14) was screened for HIF2a PAS B binding using $^1\text{H}/^{15}\text{N}$ -HSQC NMR; as seen in Figure 1, 21 hits were obtained for HIF2a PAS B (see also, Specification, p.18, line 1). From these the inventors developed a "lead" HIF2a PAS B ligand (Specification, top of p.31).

The practitioner does not require any a priori structural characteristics of the recited "foreign ligand" to practice the method. As demonstrated, the method is typically practiced using a library of compounds which need not be structurally characterized.

As for the cited step of introducing into the foreign ligand into the hydrophobic core of the PAS domain, this can be effected by simply mixing a PAS domain-containing protein with the ligand in solution (Specification, p.20, lines 7-8).

As demonstrated by the Specification (supra) and the uncontroverted expert declaration of record, one skilled in the art would have been readily able to practice this without undue experimentation.

35USC112, first paragraph (written description)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein the PAS domain is HIF2a PAS B....

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The practitioner does not require any a priori structural characteristics of the recited "foreign ligand" to practice the method. As demonstrated, the method is typically practiced using a library of compounds which need not be structurally characterized.

As demonstrated by the Specification (supra) and the uncontested expert declaration of record, the Specification amply describes and exemplifies the claimed methods to one skilled in the art.

35USC103(a)

The claims are directed to a method of changing a functional surface binding specificity of a selected PAS domain, wherein the PAS domain is folded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity by (a) introducing into the hydrophobic core of the PAS domain a foreign ligand of the PAS domain; and (b) detecting a resultant change in the functional surface binding specificity of the PAS domain, wherein the PAS domain is HIF2a PAS B, and the binding specificity is an intramolecular binding affinity of the PAS domain detected as a change in chemical shifts detected by 1H/15N-HSQC NMR....

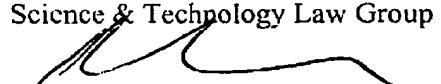
Vogtherr (2003) generally describes the use of NMR-based screening for lead discovery; Amezcua (2002) describes the use of NMR to detect ligand binding to PAS kinase; Ema (1997) reports that *HIF1a* heterodimerizes with Arnt (note that HIF1a is structurally and functionally distinct from the recited HIF2a; Sowter 2003, attached); and Fukunaga (1995) reports identification of functional domains of the aryl hydrocarbon receptor.

Prior to the present disclosure, HIF was known to be regulated in several ways by oxygen availability, but only via mechanisms that are based on oxygen-sensitive enzymes that covalently modify portions of the HIF_a subunit at sites distant to the PAS domains (Bruick & McKnight, *Science* 294(2001): 1337; Jaakkola et al., *Science* 292(2001): 468-472; Ivan et al., *Science* 292(2001): 464-468; Lando et al., *Science* 295(2002): 858-861). These prior findings taught away from any expectation that the HIF PAS domains would be sensory. In addition, HIF2a PASB presents a well-folded domain lacking the dynamic regions of PASK PAS A (Ameszcu et al., 2002, p.1352, col.1, lines 10-12) and long insertion loops of NPAS2 PAS A (Erbel et al., 2003, attached), further removing any expectation of core ligand binding. Furthermore, we have of record uncontested evidence in the form of an expert Declaration, confirming that one skilled in the art at the time of our filing would not have expected HIF2a PAS to provide a core for sensory ligand binding.

The Action correctly states that the inventors' prior publication (Amezucua et al., 2002) disclosed that hPASK PAS A has a well-packed hydrophobic core, yet was able to bind small organic molecules, and speculated that a broad range of PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo. However, as noted above, hPASK PAS A also demonstrated "unusual flexibility ... near the ligand binding sites" (Amezucua et al., 2002, p.1352, col.1, lines 10-12). This unusual flexibility near the ligand binding site is what led the authors to hypothesize that hPASK PAS A might be able to bind small organic molecules despite its NMR-apparent well-packed core (id.) -- and this unusual flexibility near the ligand binding site is not present in HIF2a PASB. Also as noted above, unlike the situation with hPASK, HIF was previously known to be regulated by non-PAS mechanisms. It is because of their structural and functional distinctions, that there is no suggestion anywhere that HIF2a PAS would or could provide a receptor for small organic molecules, and no one skilled in the art would try to impose on HIF2a PASB an inference drawn from a functionally and structurally distinct protein like HPASK PAS A. And the foregoing is documented in the uncontested expert declaration of record.

The Examiner is invited to call the undersigned with any suggestions for amending the claims or further clarifying any of the foregoing. Please charge any required fee for this communication to our Dep. Acct. No. 19-0750 (order UTSD:1510-1).

Respectfully submitted,
Science & Technology Law Group



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